Expanded Newborn Screening:
Changing the Face of Inborn Errors of Metabolism

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Sponsored by Wayne State University School of Medicine

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Inborn Errors of Metabolism (IEM)

- Over the last 25 years the field of metabolic diseases has evolved from a limited number of rare, untreatable, often fatal disorders to a field of acutely life-threatening but, for a substantial number, treatable diseases.

Inborn Errors of Metabolism

- Early recognition and prompt treatment remain critical.
- Early signs and symptoms are often very non-specific.
- Episodes of metabolic decompensation can lead to irreversible neurologic impairment.


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"Excuse me! Can we get a little Newborn Screening over here?"
Click here to learn how you can help!

Expanded Newborn Screening:
Changing the Face of Inborn Errors of Metabolism

- Robert Grier, PhD
  - History and Future of NBS in MI
  - Tandem Mass Spectrometry

Michigan Newborn Screening History

- 1965
  - Phenylketonuria
- 1977
  - Congenital Hypothyroidism
- 1984
  - Galactosemia
- 1987
  - Biotinidase Deficiency
  - Maple Syrup Urine Disease
  - Hemoglobinopathies
- 1993
  - Congenital Adrenal Hyperplasia
- 2003
  - Medium Chain Acyl-Coenzyme A Dehydrogenase Deficiency (MCAD)
- 2004
  - Homocystinuria
  - Citrullinemia
  - Argininosuccinic Aciduria
  - Tyrosinemia
- 2005
  - Expanded Screening Pilot

Screening Recommendations

- Initial screen at 24-36 hours of age
- Test before discharge or transfer regardless of age
  - Follow directions on Early Specimen letter from the State Laboratory regarding repeat specimens
- Test before transfusion of red blood cells or the administration of TPN
- Specific screening guidelines for NICU population

Tandem Mass Spectrometry (MS/MS)

- Molecules are detected by measuring their weight
- Can test for many disorders with a single blood spot
- Shorter run times per sample
- Additional disorders added at a relatively low cost

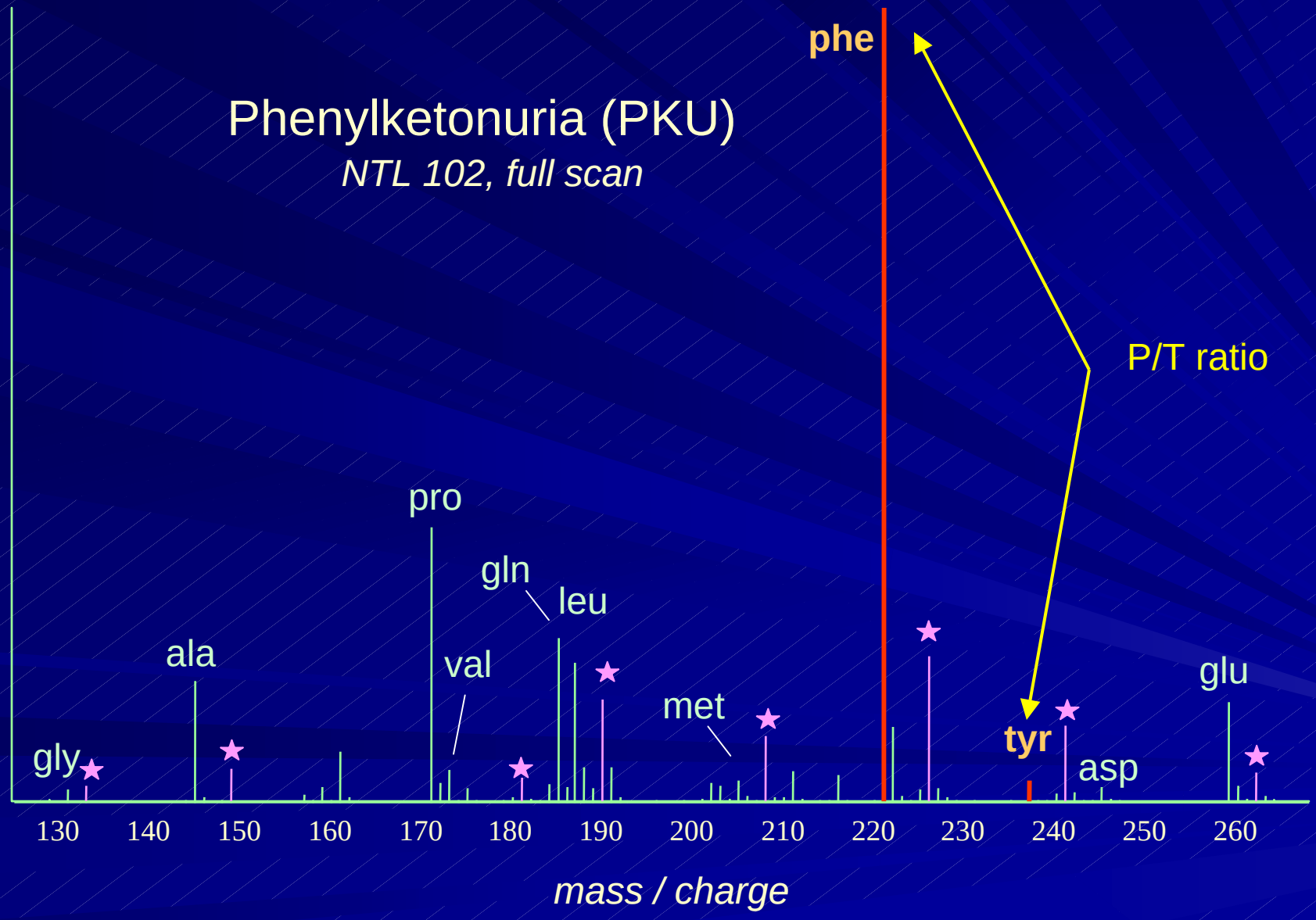
Newborn Screening
Today

- Tandem Mass Spectrometry
  - Fatty Acid Disorders
    - MCAD, VLCAD, LCHAD, GA 11, etc.
  - Amino Acid Disorders
    - PKU, MSUD, TYR, CIT, ASA, etc.
  - Organic Acid Disorders
    - PA, MMA, IVA, GA1, 3MCC, etc.

Tandem MS of Amino Acids

- Challenge:
  - Analyze 9 amino acids from a few µL of blood that is dried on filter paper.
  - Analyze 500 specimens per instrument per day.
  - Minimize False Results
    - No False Negative Results
    - Minimal False Positive Results

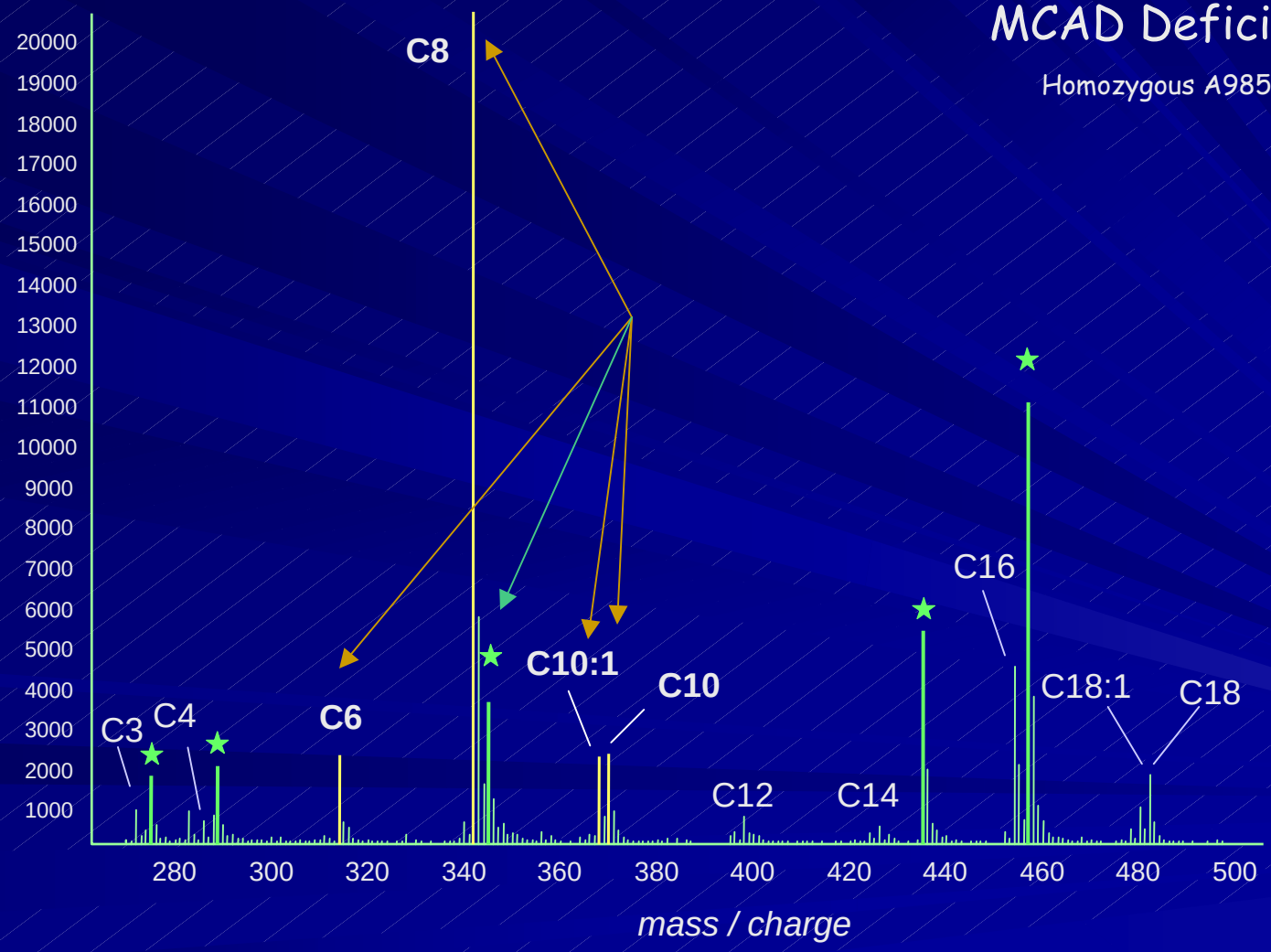
Diagnosis: PKU



Tandem MS of Acylcarnitines

- Challenge:
  - Analyze 40 + diagnostically important acylcarnitines from a few µL of dried blood on filter paper.
  - Analyze 500 specimens per instrument per day.
  - Minimize False Results
    - No False Negative Results
    - Minimal False Positive Results

Diagnosis: MCAD Deficiency



MS/MS Interpretation

- Visual and Quantitative Interpretation
  - Analyze the abnormal printouts each day by Scientist at the Lansing NBS Lab with initial interpretation
  - Contact Dr. Grier or Children's Hospital of MI Geneticist for confirmation of interpretation
  - Request repeat analysis for newborn specimens that may be borderline, suspicious or unsatisfactory
  - Determine interpretation for positive data, with referral to Geneticist on-call at Children's Hospital of MI
  - Monitor internal standards and response of the MS/MS

Expanded Newborn Screening:
Changing the Face of Inborn Errors of Metabolism

- Ayesha Ahmad, MD
  - Process involved in screening and follow-up
  - Services offered by CHMMC
  - An overview of IEM's

Michigan Newborn Screening Law

MCL 333.5431

Highlighted Features:

- No informed consent required
- Department may require that the tests be performed by the department
- Violation is a misdemeanor
- Fee for testing

Components of Program

Hospitals
Midwives

Families

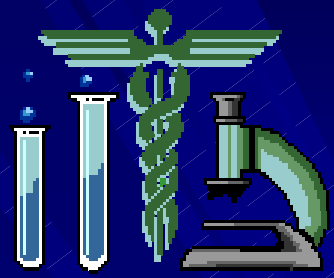
Medical Home

Newborn
Screening
Follow up

Newborn
Screening
Laboratory

Medical
Management
Services

Laboratory Procedures



- Specimens are tested the day they are received
  - Up to 700 specimens each day
- Preliminary results same day for life threatening disorders
- Unsatisfactory specimens reported the same day they are received
  - All tested and positives reported

Specimen Retention and Disposal

- Specimens are stored for 21½ years, then destroyed
- Parents/legal guardians may request:
  - Disposal of a specimen prior to the end of the retention schedule
  - Use of specimen for forensic, diagnostic or research purposes

The Newborn Screening Laboratory screens all Michigan neonates for **forty-eight** disorders.

NOTICE: Effective May 1, 2006, all disorders will be included on the notification of screening results.

ACMG/HRSA Approved NBS Panel

Amino Acid Disorders:

- Phenylketonuria (PKU)
- Benign hyperphenylalaninemia (HYPER-PHE)
- Biopterin cofactor biosysnthesis (BIOPT (BS))
- Defects of biopterin cofactor regeneration (BIOPT(REG))
- Maple syrup disease (MSUD)
- Homocystinuria
- Hypermethioninemia (HCY/MET)
- Citrullinemia (CIT)
- Citrullinemia Type II (CIT II)
- Argininosuccinic acidemia (ASA)
- Tyrosinemia Type I (TYR I)
- Argininemia (ARG)

ACMG/HRSA Approved NBS Panel

Fatty Acid Oxidation Disorders:

- Carnitine:acylcarnitine translocase deficiency (CACT)
- Carnitine palmitoyltransferase II deficiency (CPT II)
- Carnitine uptake defect (CUD)
- Carnitine palmitoyltransferase I def. (liver) (CPT 1A)
- Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
- Glutaric academia type II (GA II)
- Med.-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Long-chain L-3-OH acyl-CoA de hydrogenase deficiency (LCHAD)
- Trifunctional protein def.(LCHAD/TFP)
- Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Med.-chain ketoacyl-CoA thiolase deficiency (MCKAT)
- Med./short-chain L-3-OH acyl-CoA dehydrogenase deficiency (M/SCHAD)
- Dienoyl-CoA reductase deficiency (DE RED)

ACMG/HRSA Approved NBS Panel

Organic Acid Disorders:

- Isovaleric academia (IVA)
- 2-Methyl butyryrl-CoA dehydrogenase deficiency (2MBG)
- 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
- 3-OH 3-CH3 glutaric aciduria (HMG)
- 3-Methylglutaconic aciduria (3MGA)
- Beta-ketothiolase deficiency (BKT)
- Glutaric acidemia type I (GA I)
- Propionic academia (PA)
- Methylmalonic acidemia (mutase deficiency) (MUT)
- Methylmalonic acidemia (Cbl A,B)
- Methylmalonic acidemia (Cbl C,D)
- Multiple carboxylase deficiency (MCD)
- 2-Methyl 3-hydroxy butyric aciduria (2M3HBA)
- Malonic acidemia (MAL)
- Isobutyryl-CoA dehydrogenase deficiency (IBG)

ACMG/HRSA Approved NBS Panel

Endocrine Disorders:

- Congenital Adrenal Hyperplasia (CAH)
- Congenital Hypothyroidism (CH)

Enzyme Disorders:

- Galactosemia (GALT)
- Biotinidase Deficiency (BIOT)

Hemoglobinopathies:

- Sickle cell anemia (Hb SS)
- Hb S/C Disease (Hb S/C)
- Hb S/Beta-thalassemia (Hb S/Beta-Th)
- Variant Hb-pathies (Var Hb)

Follow-Up

- Positive results are followed up with a repeat screening test or prompt referral to medical management
- Telephone/fax notification with instructions to local physician
- Negative results sent to hospital
  - Hospital forwards the "Physician copy" to physician documented on the NBS card
  - Hospital places "Submitter copy" in the infant's medical record

Medical Management

- Children's Hospital of Michigan Metabolic Clinic (CHMMC) at the Detroit Medical Center, Wayne State University, designated as the site in the state of MI for diagnostic confirmation, management and follow-up of all newborns identified with a metabolic disease by NBS.
- All strong positive NB screens for Inborn Errors of Metabolism (IEM) referred to CHMMC.
- (Change in site on October 1, 2004).

The Children's Hospital of Michigan Metabolic Clinic

The Team

- Metabolic Geneticists
  Jerry Feldman, MD, PhD: Program Director
  Ayesha Ahmad, MD: Clinical Director, CHMMC
  Erawati Bawle, MD: Division Director, Genetic and Metabolic Disorders
  Laura Martin, MD
- Metabolic Laboratory Director, DMC: Robert Grier, PhD
- Coordinator/Genetic Counselor: Peggy Rush, MS, CGC
- Metabolic Nurse: Denise Pleger, RN
- Metabolic Dieticians: June Ventimiglia, RD
  Heidi Edwards, RD
- Clinical Psychologist: Sara Brown, MA/TLLP
- Social Worker: Ellen Podeszwa, MSW
- Medical Secretary: Sparkle Wall

For all strong positive screens for an IEM:

- CHMMC staff contacts primary medical doctor identified on NBS card with recommendations:
  - Recommend time frame for primary doctor to evaluate the neonate.
  - Detailed information on laboratory investigations needed for confirmation including information on sample collection and shipment.

Note: Patients can be referred to CHMMC for confirmatory labs if geographically possible.

  - Initiation of treatment/ intervention as appropriate.
  - Information on suspected IEM.

For all strong positive screens for an IEM:

- CHMMC Staff Recommendations cont.
  - 24 hr contact information for on-call metabolic geneticist.
  - Immediate referral/transfer to CHM if primary doctor feels it is clinically indicated/ based on disorder.
  - 24 hr metabolic consultation to admitting physicians if patient admitted to a tertiary care hospital, locally.
  - Referral to CHMMC when disorder is confirmed.

After confirmation of metabolic disorder:

- Referral to CHMMC for:
  - Detailed evaluation
  - Further diagnostic testing (enzymatic/ molecular confirmation) as appropriate, may be pursued at CHMMC.
  - Management (multidisciplinary approach)
  - Genetic counseling
  - Disorder/ diet and life-style education
  - Provision of emergency protocol

Inborn Errors of Metabolism:
Recognition

Why is diagnosis difficult?

- Signs and symptoms are often non-specific especially in neonates.
- Other neonatal conditions like sepsis, CHD, GI obstruction present with similar symptoms.
- IEM's not usually considered in acute situations.
- Neonatal deaths may be attributed to SIDS or infection.
- Almost all IEM are recessive disorders;
  - Isolated cases common in sib-ships
- May not present until later in life.

Signs and Symptoms of IEM's in Neonates

- Lethargy, inactivity, irritability
- Reduced appetite, spitting up, vomiting
- Apnea, tachypnea
- Seizures
- Hypothermia, hyperthermia
- Hypoglycemia
- Metabolic acidosis
- Jaundice or hepatomegaly
- Unusual odors

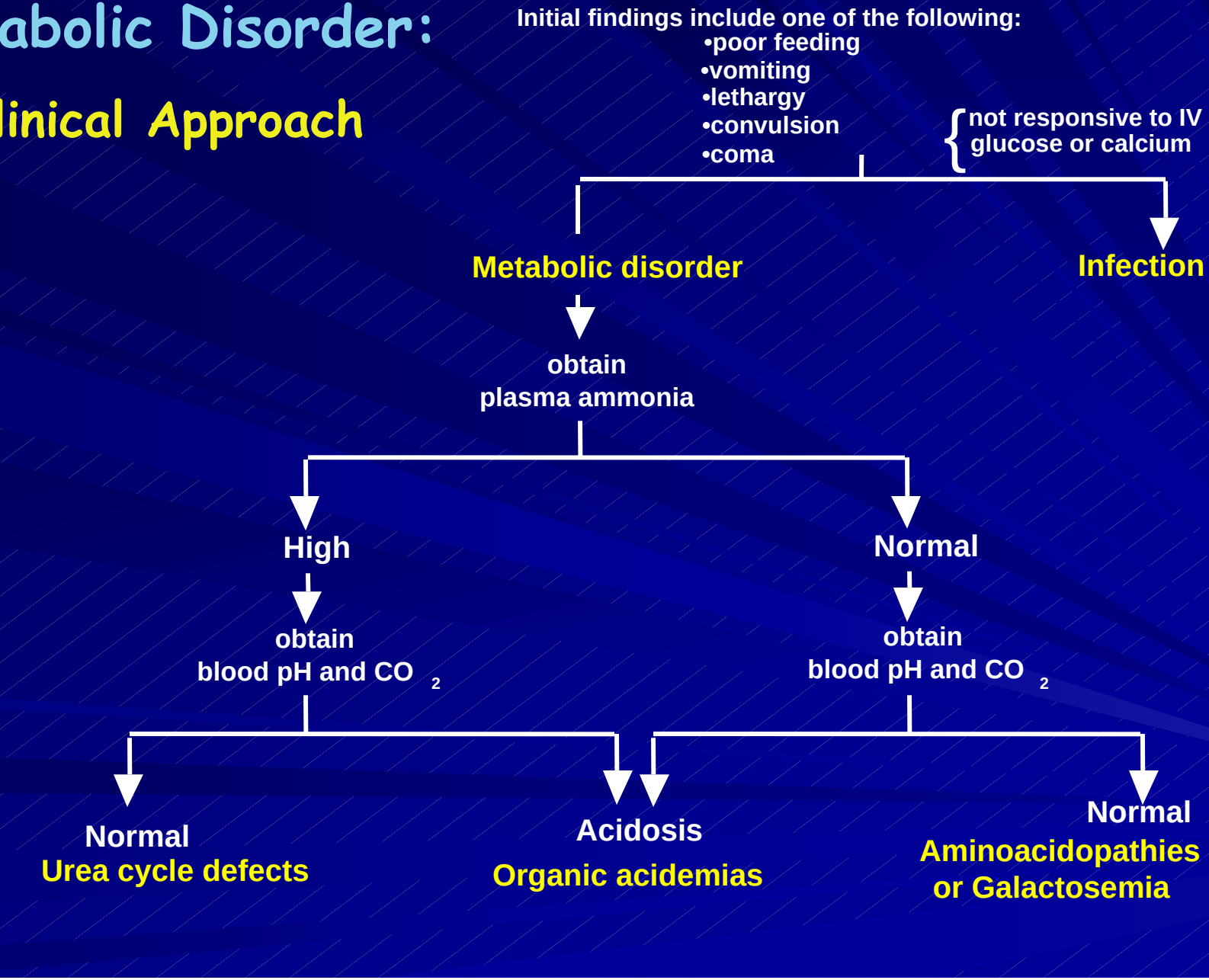
General Diagnostic Approach
Initial Screening Tests

Blood:
- CBC with Diff
- Blood gas
- Serum electrolytes
- Blood glucose
- Plasma ammonia
- Plasma Lactic acid

Urine:
- Reducing substances
- Ketones

Suspected Metabolic Disorder:

Clinical Approach



Diagnostic Approach
Advanced Screening Tests

Blood:

- Plasma amino acids
- Plasma acylcarnitine profile
- Free and total carnitine

Urine:

- Organic acids
- Acylglycine profile
- Amino acids

Enzyme assays

Molecular tests

Treatment of IEM's:
General Principles

- Halt catabolism: provide adequate glucose
- Stop dietary source of offending substrate: protein/formula (lactose/galactose)
- Treat metabolic emergencies that are life-threatening:
  - Hyperammonemia
  - Metabolic Acidosis
  - Hypoglycemia

Treatment of IEM's:
General Principles cont.

- Supportive care: search for and treat infections
- Toxin removal: hemodialysis
- Make specific diagnosis to institute additional therapies:
  - Allow outlet by alternative pathways
  - Include vitamin/ co-factor supplementation
  - Carnitine, specific substrates

Inborn Errors Of Metabolism:
Genetic Counseling Issues

- Essential to provide genetic counseling after diagnosis is made
- Most IEM's are autosomal recessive
- Issues to discuss:
  - Recurrence risks
  - Risks to other children/family members
  - Carrier testing, if available
  - Prenatal diagnosis options for future pregnancies

Diseases Detectable By Tandem Mass Spectrometry

Amino Acid Screen	Phenylketonuria, tyrosinemia, homocystinuria, maple syrup urine disease (MSUD)
Urea Cycle	**Citrullinemia, Argininosuccinic acidemia (ASA), Argininemia.**
Acyl-carnitine screen	Organic Acidemias Fatty Acid Oxidation Disorders.

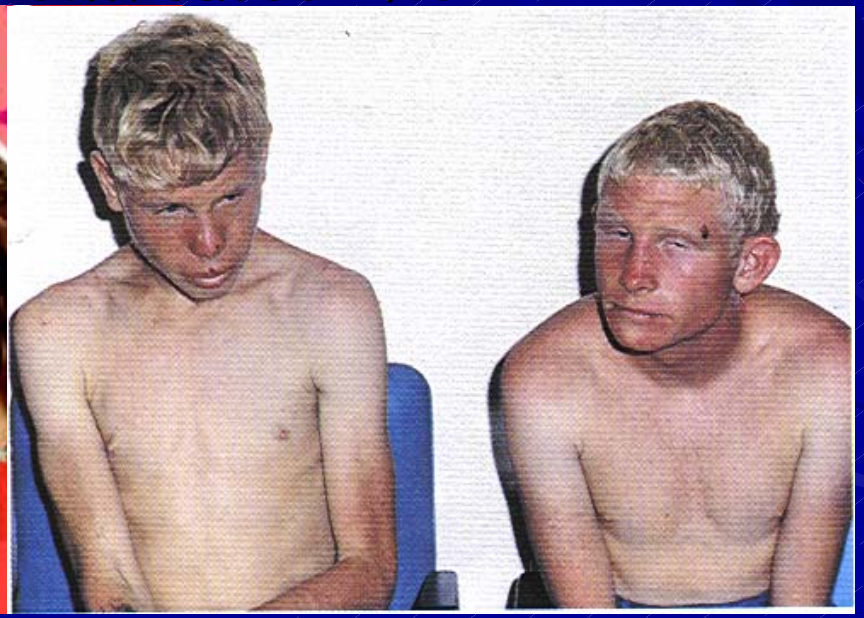
Amino Acid Disorders

Screening for PKU (started in 1960's): The Quest Against Mental Retardation

Treated PKU

From PKU.com

Untreated PKU



From Atlas of Metabolic Diseases, Nyhan and Ozand, 1998

Other Amino Acid Disorders

Examples: Tyrosinemia Type 1 and Homocystinuria

- Goal of screening
  - Rapid and pre-symptomatic identification of affected infants to prevent neurological impairment; reduction of morbidity and mortality.
- Diagnosis (Based on suspected disorder)
  - plasma amino acids
  - may also need urine amino acids and urine organic acids.

Other Amino Acid Disorders
Examples: Tyrosinemia Type 1 and Homocystinuria

- Treatment
  - Strict diet limiting the intake of offending (precursor) amino acid/protein restriction.
  - Use of special metabolic formulas/ supplements
  - Specific therapy based on definitive diagnosis
    - NTBC for Tyrosinemia Type 1
    - Use of vitamins/co-factors for homocystinuria

Urea Cycle Disorders:
Citrullinemia and Argininosuccinic Acidemia

- Goal of Screening
  - Prompt identification and treatment reducing subsequent morbidity and mortality
- Diagnosis
  - Ammonia level STAT
    (other acute laboratory tests as clinically indicated)
  - Plasma and urine amino acids
  - Urine organic acids

Note: The newborn screening test can not differentiate Citrullinemia from Argininosuccinic Acidemia (ASA). Further diagnostic testing is needed. Proximal urea cycle disorders like OTC and CPS deficiencies are not diagnosed by current NBS.

Urea Cycle Disorders:
Citrullinemia and Argininosuccinic Acidemia

- Treatment
  - Special diet:
    - protein restriction
    - appropriate amino acid supplements
  - Medications to remove substrates using alternate pathways
  - Dialysis may be necessary during episodes of hyperammonemia
  - Avoidance of catabolism
  - Use of emergency protocol

Fatty Acid Oxidation Disorders (FOD's)

- Goal of Screening
  - Prompt identification and treatment reducing subsequent morbidity and mortality. Prevention of hypoglycemia that could lead to coma, encephalopathy, liver failure, myopathy or death
- Diagnosis (based on suspected disorder)
  - Plasma acylcarnitine profile
  - Urine acylglycine profile/ and urine organic acids
  - Serum free and total carnitine levels
  - Other labs as clinically indicated: glucose, electrolytes, LFT's

Note: confirmatory tests (especially for long chain FOD's) may be normal when patient not stressed. Confirmation may require enzyme assay.

Fatty Acid Oxidation Disorders (FOD's)

- Treatment
  - Frequent feedings are instituted to avoid fasting
  - Emergency plan for times of poor oral intake or intercurrent illness
  - Low-fat/high-carbohydrate diet and supplemental carnitine may be used.
    - Carnitine is generally not advocated for long chain FOD's.

Organic Acidemias

- Goal of Screening
  - Prompt identification and treatment reducing subsequent morbidity and mortality
- Diagnosis
  - Urine organic acids
  - Other tests based on suspected disorder: plasma acylcarnitine profile, urine acylglycine profile
  - Additional labs as clinically indicated: ammonia level, lactic acid, glucose, urine ketones.

Organic Acidemias

- Treatment
  - Special diet/protein restriction
  - Co-factor supplements
  - Carnitine supplements
  - Avoidance of catabolism
  - Use of emergency protocol

Newborn Screening in Michigan:
Disease Incidence in 2003

- PKU - 14
  - 7 diet treated
- Hypothyroidism – 85
- Galactosemia - 1
- MSUD - 1
- Biotinidase – 15
  - 1 Profound
  - 14 Partial
- Sickle Cell Diseases - 69
  - FS- 38
  - FSA- 12
  - FSC-17
  - FSD- 1
  - FSV- 1
- CAH - 4
- MCAD – 5 (plus 1 sibling)

Total Infants Identified: 194

Combined Incidence: 1 per 650 births

Metabolic Disorder Incidence in 2003: 1 per 3500 births

Metabolic Disorders Identified in 2005

- PKU: 10
- GALT: 4
- Biotinidase: 19
- MCAD: 9
- CIT/ASA: 3
- CUD: 1
- SCAD: 1
- VLCAD: 3
- 2MBG:1
- PA:1
- Maternal 3MCC:1

Metabolic Disorder Incidence in 2005: 1 per 2500 births

Michigan Department of Community Health

Newborn Screening Program

- NBS Program
  - Phone: 517-335-9205 or 866-673-9939
  - www.michigan.gov/newbornscreening
- NBS Coordinator
  - Tammy Ashley, RN, MSN
    517-335-8959
    ashleyt1@michigan.gov
- NBS Nurse Consultant/Educator
  - Midge McCaustland, RNC, MSN
    517-335-8588
    mccaustlandm@michigan.gov

The Children's Hospital of Michigan Metabolic Clinic (CHMMC)

- Phone: 313-745-4513
- Toll Free: 866-44CHMMC
  (866-442-4662)
- For the on call metabolic geneticist:
  - Dial 313-745-0203
  - Followed by pager #96025
  - Followed by your call back number.

Additional Resources

- American College of Medical Genetics
  - ACT Sheets and Confirmatory Algorithms
  - *"Intermediate Management Guidelines for Newborn Screening."*
  - www.acmg.net
- *Pediatrics*, Vol. 117 No. 5 May 2006, pp.i
  - A Look at Newborn Screening: Today and Tomorrow
  - pediatrics.aappublications.org/current.shtml
- Michigan's Genetics Resource Center
  - Newborn Screening
  - www.migeneticsconnection.org/newborn.shtml

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